THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 21

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MICHAEL G. ROSENBLUM
and
NICHOLAS J. DONATO

Appeal No. 1997-3945
Application No. 08/410,390[1]

ON BRIEF

Before WINTERS, WILLIAM F. SMITH and ROBINSON, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

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[1] Application for patent filed March 27, 1995. According to appellants, this application is a continuation of Application No. 08/192,655, filed February 7, 1994, now abandoned.

DECISION ON APPEAL

This appeal was taken from the examiner's decision rejecting claims 1 through 4 and 17 through 20. Claims 5, 8 through 16, 21, and 24, which are the only other claims remaining in the application, stand withdrawn from further consideration by the examiner as directed to a non-elected invention. Claims 1 and 17 are illustrative of the subject matter on appeal and read as follows:

1. An immunoconjugate coupled through the avidin-biotin interaction, comprising an internalizable cell binding component having a biotin-binding element conjugated to a biotinylated moiety, wherein said biotinylated moiety is selected from the group consisting of cytotoxic proteins and nucleic acids, wherein said protein is selected from the group consisting of gelonin, ricin, saporin, abrin, diptheria toxin, psuedomonas [sic] exotoxin, rayalase, superoxide dismutase, protein tyrosine phosphatase, protein phosphatase (PP-1 or PP-2), protein kinase A and protein kinase C.

17. A method of delivering a cytotoxic moiety to a cell comprising the administration of an immunoconjugate coupled through the avidin-biotin interaction to a human, wherein said immunoconjugate comprises an internalizable cell binding component having a biotin-binding element conjugated to a biotinylated moiety, wherein said biotinylated moiety is selected from the group consisting of cytotoxic proteins and nucleic acids, wherein said protein is selected from the group consisting of gelonin, ricin, saporin, abrin, diptheria toxin, psuedomonas [sic] exotoxin, rayalase, superoxide dismutase, protein tyrosine phosphatase, protein phosphatase (PP-1 or PP-2), protein kinase A and protein kinase C.

The references relied on by the examiner are:

Pastan et al. (Pastan '985)	4,545,985	Oct. 8, 1985
Goodwin et al. (Goodwin) (European patent application)	0,251,494	Jan. 7, 1988

Ira Pastan et al. (Pastan), "Immunotoxins," 47 Cell 641-48 (Dec. 5, 1986)

Meir Wilchek and Edward A. Bayer (Wilchek), "The Avidin-Biotin Complex in Bioanalytical Applications," 171 Analytical Biochemistry 1-32 (1988)

Olivia Martinez et al. (Martinez), "Variance in cytotoxic effectiveness of antibody-toxin A hybrids," 1 Cancer Surveys no. 3, 374-88 (1982)

Claims 1 through 4 stand rejected under 35 U.S.C. § 103 as unpatentable over Martinez in view of Pastan ('985), Goodwin, Pastan (Cell), and Wilchek.

Claims 17 through 20 stand rejected under 35 U.S.C. § 103 as unpatentable over Pastan ('985) in view of Martinez, Wilchek, and Goodwin.

On consideration of the record, we reverse the rejections of claims 1 through 4 and 17 through 20 under 35 U.S.C. § 103. Under the provisions of 37 CFR § 1.196(b), we enter a new ground of rejection of claims 1 through 4 under 35 U.S.C. § 103.

Claims 1 through 4

We agree with the examiner’s conclusion that the product recited in claims 1 through 4 would have been obvious to a person having ordinary skill in the art. We disagree, however, with the examiner's interpretation of these claims and with the reasoning set forth in the Answer (Paper No. 17). In reaching our decision in this appeal, we have carefully

considered appellants' specification and claims, the applied references, and the respective positions articulated by appellants and the examiner. In our judgment, some, but not all, of the references cited by the examiner are relevant. Under these circumstances, we reverse the examiner's rejection of claims 1 through 4 on procedural grounds and we enter a new ground of rejection of those claims under the provisions of 37 CFR § 1.196(b).

Claims 1 through 4 are rejected under 35 U.S.C. § 103 as unpatentable over the combined disclosures of Goodwin, Pastan '985, and Pastan (Cell).

The claimed invention is directed to an immunoconjugate coupled through the avidin-biotin interaction, comprising an internalizable cell binding component having a biotin-binding element conjugated to a biotinylated moiety. The biotinylated moiety is selected from the Markush group of cytotoxic proteins and nucleic acids, wherein the cytotoxic protein is further selected from the group consisting of gelonin, ricin, saporin, abrin, diptheria toxin, pseudomonas exotoxin, rayalase, superoxide dismutase, protein tyrosine phosphatase, protein phosphatase (PP-1 or PP-2), protein kinase A and

protein kinase C. The cell binding component (element) may be, for example, a monoclonal antibody. See page 5, third paragraph of the specification and see dependent claim 3. The biotin-binding element is any chemical that binds biotin, e.g., avidin, streptavidin or analogues of avidin or streptavidin. See page 5, second paragraph of the specification and see dependent claim 2.

As recited in claim 1 on appeal, the immunoconjugate comprises an "internalizable" cell binding component coupled through the avidin-biotin interaction, but the claim does not require that the immunoconjugate be preformed. The "internalizable" characteristic is discussed in the specification, page 12, lines 15 through 18.

> The ability of A108-avidin to bind biotin and internalize into eukaryotic cells can be demonstrated utilizing a biotinylated protein having toxic activity only when internalized into cells (e.g., the plant protein, gelonin).

The toxicity of appellants' immunoconjugate becomes apparent when internalization in cells occurs. When the cell binding component and the biotinylated moiety are coupled through the avidin-biotin interaction, an immunoconjugate is produced.

Internalization of the immunoconjugate is evidenced by its ability to transfer toxin (of the biotinylated moiety) into a receptor cell where it is capable of inducing cytotoxicity, thus demonstrating successful binding of the components through the avidin-biotin interaction. We find no language in claims 1 through 4, however, requiring that appellants' immunoconjugate be preformed. The claims "read on" an immunoconjugate coupled through the avidin-biotin interaction after the sequential administration of an internalizable cell binding component having a biotin-binding element and a biotinylated moiety. Stated another way, claims 1 through 4 embrace an immunoconjugate preformed in vitro before the administration to a human or where the avidin-biotin interaction takes place in vivo after the administration to a human.

Goodwin discloses a system for targeting a therapeutic or diagnostic agent at a specific internal body site, e.g., a solid tumor. The targeted agent is a biotinylated compound having a pharmaceutically active therapeutic or diagnostic moiety (the active moiety). See Goodwin, page 3, last paragraph. Goodwin discloses that the active moiety may be,

inter alia, a toxin (page 4, lines 1 through 3). Goodwin's system includes (1) the biotinylated compound (page 3, line 50 through page 4, line 28); (2) an avidin-containing binding protein capable of localizing selectively at the target site, when administered parenterally (page 4, line 30 through page 5, line 20); and (3) a clearing agent (page 5, lines 25 through 35). The avidin-containing binding protein serves both as a targeting agent capable of localizing specifically at an internal target site, and as an agent for binding the biotinylated compound to the target site through the avidin-biotin interaction. The binding protein may be, for example, a monoclonal antibody (page 5, lines 5 through 14).

Goodwin further discloses a method for targeting a therapeutic or diagnostic agent to a selected internal body site, e.g., a solid tumor, by sequentially administering the avidin-containing binding protein; the clearing agent; and the biotinylated compound. In the passage at page 5, lines 50 through 52, Goodwin makes clear that these components are administered sequentially:

> According to an important advantage of the method, the binding protein is delivered in non-complexed form, i.e., without bound biotinylated

> compound so that the treated individual is not exposed to the compound during the extended period of protein localization at the tumor site.

According to Goodwin, the avidin-biotin interaction takes place in vivo after the sequential administration of Goodwin's components to a treated individual.

The immunoconjugate of claim 1 differs from the product disclosed by Goodwin in that Goodwin's biotinylated compound includes a pharmaceutically active toxin moiety, whereas claim 1 recites a biotinylated moiety selected from the group consisting of cytotoxic proteins and nucleic acids, where said protein is selected from the group consisting of gelonin, ricin, saporin, abrin, diptheria toxin, *Pseudomonas* exotoxin, rayalase, superoxide dismutase, protein tyrosine phosphatase, protein phosphatase (PP-1 or PP-2), protein kinase A and protein kinase C. Goodwin discloses, generically, a pharmaceutically active toxin moiety, whereas claim 1 recites species of cytotoxic proteins.

Pastan '985 discloses a method of chemically modifying Pseudomonas exotoxin (PE) so that, after conjugating the exotoxin to a monoclonal antibody (ab) such as the antibody to the transferrin receptor, the PE-ab conjugate becomes a highly

potent immunotoxin suitable for use against human tumor cells. Figure 1 of Pastan (Cell), page 643, is entitled "Pathway of Immunotoxin Entry," illustrating the pathway by which immunotoxins are internalized into cells. This reference suggests that immunotoxins composed of antibodies to the human transferrin receptor and either ricin A chain or Pseudomonas exotoxin A are very effective. See Pastan (Cell), page 646, second column, first full paragraph.

We are persuaded that a person having ordinary skill in the art, armed with the disclosures of Pastan '985 and Pastan (Cell), would have found it obvious to modify the biotinylated compound of Goodwin by using Pseudomonas exotoxin as the pharmaceutically active moiety therein. By thus modifying the system of Goodwin, per the teachings of Pastan '985 and Pastan (Cell), the hypothetical person having ordinary skill in this art would have arrived at the subject matter sought to be patented in claim 1 where the cytotoxic protein is Pseudomonas exotoxin. Such hypothetical person would have had a reasonable expectation of achieving a pharmaceutically active immunoconjugate coupled through the avidin-biotin interaction, where the interaction takes place in vivo after the

administration of system components to a human. Again, claim 1 "reads on" an immunoconjugate where the avidin-biotin interaction takes place in vivo.

Accordingly, we conclude that the subject matter sought to be patented in claim 1 would have been obvious within the meaning of 35 U.S.C. § 103 based on the combined disclosures of Goodwin, Pastan '985, and Pastan (Cell).

The limitations of dependent claims 2 through 4 are also found in Goodwin, Pastan '985, and Pastan (Cell). See particularly Goodwin, page 4, line 46, disclosing avidin and streptavidin. Compare the recitation in claim 2 on appeal where "said biotin-binding element is selected from the group consisting of avidin, streptavidin or analogues of avidin or streptavidin." Further see Goodwin, page 5, line 10 and Pastan (Cell), page 643, Figure 1, disclosing the use of a monoclonal antibody. Compare the recitation in claim 3 on appeal where "said cell binding element is a monoclonal antibody." Finally, see Pastan '985, column 2, lines 62 through 68, disclosing monoclonal antibodies against the transferrin receptor. Compare the recitation in claim 4 on appeal "wherein said monoclonal antibody specifically binds an

antigen selected from the group consisting of . . . transferrin receptor." We conclude that the subject matter sought to be patented in dependent claims 2 through 4, considered as a whole, would have been obvious within the meaning of 35 U.S.C. § 103 based on the combined disclosures of Goodwin, Pastan '985, and Pastan (Cell).

The examiner's rejection of claims 1 through 4 is reversed. For the reasons set forth above, we enter a new ground of rejection of those claims under 35 U.S.C. § 103 as unpatentable over the combined disclosures of Goodwin, Pastan '985, and Pastan (Cell).

Claims 17 through 20

Method claims 17 through 20 differ from product claims 1 through 4 in one significant respect, namely, the former claims require that appellants' immunoconjugate be preformed. This follows because independent claim 17 recites a method of delivering a cytotoxic moiety to a cell comprising "the administration of an immunoconjugate coupled through the avidin-biotin interaction to a human, wherein said immunoconjugate comprises an internalizable cell binding

component having a biotin-binding element conjugated to a biotinylated moiety" wherein the biotinylated moiety is defined in Markush group format. We think it clear that claim 17, by its very terms, requires that the immunoconjugate be preformed, i.e., "coupled through the avidin-biotin interaction," before the immunoconjugate is administered to a human.

As previously discussed, Goodwin discloses sequentially administering the avidin-containing binding protein, the clearing agent, and the biotinylated compound disclosed therein. In the passage at page 5, lines 50 through 52, Goodwin makes clear that these components are administered sequentially:

> According to an important advantage of the method, the binding protein is delivered in non-complexed form, i.e., without bound biotinylated compound so that the treated individual is not exposed to the compound during the extended period of protein localization at the tumor site.

Likewise, Martinez discloses sequentially administering biotin-coupled anti-mouse cell surface antibodies and avidin-diphtheria toxin. See Martinez, page 377, first full paragraph.

Therefore, the combined disclosures of Goodwin and Martinez, regardless how viewed, would not have led a person having ordinary skill in the art to the method recited in claims 17 through 20 requiring that appellants' immunoconjugate be preformed. Furthermore, we find no teaching, suggestion, or disclosure in Pastan '985 or Wilchek which would cure the above-noted deficiency of the combined disclosures of Goodwin and Martinez. For this reason, the rejection of claims 17 through 20 under 35 U.S.C. § 103 as unpatentable over Pastan '985 in view of Martinez, Wilchek, and Goodwin is reversed.

Procedural Matters

Several procedural matters warrant attention.

Dependent claims 2 through 4 recite "[t]he non-viral vector" of claim 1 or claim 3. Independent claim 1, however, recites "[a]n immunoconjugate" and does not provide antecedent basis for "[t]he non-viral vector." Accordingly, on return of this application to the Examining Group, appellants and the examiner should consider rectifying the above-noted discrepancy in claim language, e.g., by amending claims 2 through 4 to recite "[t]he immunoconjugate" instead of "[t]he non-viral vector."

Likewise, dependent claim 3 recites "said cell binding element" whereas independent claim 1 provides antecedent basis for "an internalizable cell binding component," not a "cell binding element." Again, on return of this application to the Examining Group, we recommend that the discrepancy be rectified, e.g, by amending claim 3 to recite "said cell binding component" instead of "said cell binding element." The same infirmity besets claims 17 and 19.

Also, it appears that claim 20 should depend from claim 19, not from claim 17.

CONCLUSION

In conclusion, for the reasons set forth in the body of this opinion, we reverse the examiner's rejections of claims 1 through 4 and 17 through 20 on prior art grounds. We enter a new ground of rejection of claims 1 through 4 under 35 U.S.C. § 103 as unpatentable over the combined disclosures of Goodwin, Pastan '985, and Pastan (Cell).

This decision contains a new ground of rejection pursuant to 37 CFR § 1.196(b) (amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides, "[a] new ground of rejection shall not be considered final for purposes of judicial review."

37 CFR § 1.196(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (37 CFR § 1.197(c) as to the rejected claims:

> (1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner . . . .

> (2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record . . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED - 37 CFR § 1.196(b)

SHERMAN D. WINTERS Administrative Patent Judge	)	
WILLIAM F. SMITH Administrative Patent Judge	)	BOARD OF PATENT APPEALS AND INTERFERENCES
DOUGLAS W. ROBINSON Administrative Patent Judge	)	

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